correlation coefficient of not less than 0.99. From the graph, determine the total amount, T_U, in mg, of isopropyl alcohol in the *Assay preparation*. Calculate the percentage of isopropyl alcohol in the Dihydroxyaluminum Sodium Carbonate taken by the formula:

$$0.1T_U/W_U,$$

in which W_U is the weight, in g, of the Dihydroxyaluminum Sodium Carbonate taken. The limit is 1.0%.

Sodium content—

Potassium chloride solution—Prepare a solution of potassium chloride in water containing 38 mg per mL.

Sodium chloride stock solution—Dissolve a suitable quantity of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, in water, and dilute quantitatively and stepwise with water to obtain a solution containing 25.42 µg per mL (10.0 µg of sodium per mL).

Standard preparations—On the day of use, transfer 4.0 mL of 1 *N* hydrochloric acid and 10.0 mL of *Potassium chloride solution* to each of two 100-mL volumetric flasks. To the respective flasks add 5.0 and 10.0 mL of *Sodium chloride stock solution*. Dilute with water to volume, and mix. These solutions contain about 0.5 and 1.0 µg of sodium per mL, respectively.

Test preparation—Transfer about 250 mg of Dihydroxyaluminum Sodium Carbonate, previously dried and accurately weighed, to a 200-mL volumetric flask, add 40 mL of 1 *N* hydrochloric acid, and boil for 1 minute. Cool, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask containing 4.0 mL of 1 *N* hydrochloric acid and 10.0 mL of *Potassium chloride solution*, dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparations* and the *Test preparation* at the sodium emission line at 589.0 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-scattering* ⟨851⟩) equipped with a sodium hollow-cathode lamp and an air-acetylene flame, using as a blank a solution prepared by pipeting 4 mL of 1 *N* hydrochloric acid and 10.0 mL of *Potassium chloride solution* into a 100-mL volumetric flask, diluting with water to volume, and mixing. Plot the absorbances of the *Standard preparations* versus concentrations, in µg per mL of sodium, and draw a straight line between the plotted points. From the graph so obtained, determine the concentration, C, in µg per mL of sodium, in the *Test preparation*. Calculate the percentage of sodium in the portion of Dihydroxyaluminum Sodium Carbonate taken by the formula:

$$4000C/W,$$

in which W is the quantity, in mg, of Dihydroxyaluminum Sodium Carbonate taken: between 15.2% and 16.8% is found.

Mercury, *Method IIa* ⟨261⟩—Transfer 2.0 g to a 100-mL beaker, and add 35 mL of 1 *N* sulfuric acid: the limit is 1 ppm.

Assay—

Disodium ethylenediaminetetraacetate titrant—Dissolve 18.6 g of disodium ethylenediaminetetraacetate in water to make 500 mL, and standardize as directed in the *Assay* under *Ammonium Alum*.

Procedure—Transfer about 200 mg of undried Dihydroxyaluminum Sodium Carbonate, accurately weighed, to a 250-mL beaker, add 10 mL of 2 *N* sulfuric acid, cover the beaker, heat to 80° for 5 minutes, and boil for 1 minute. Add 25.0 mL of 0.1 *M* disodium ethylenediaminetetraacetate VS, again boil for 1 minute, cool, and then add 10 mL of acetic acid–ammonium acetate buffer TS, 50 mL of acetone, and 2 mL of dithizone TS. Using a pH meter, adjust with the addition of ammonium hydroxide to a pH of 4.5, and titrate with 0.05 *M* zinc sulfate VS, maintaining the pH at 4.5 by the addition of ammonium hydroxide as necessary, to an orange-pink color. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *M Disodium ethylenediaminetetraacetate titrant* is equivalent to 14.40 mg of CH_2AlNaO_5.

Dihydroxyaluminum Sodium Carbonate Tablets

» Dihydroxyaluminum Sodium Carbonate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of CH_2AlNaO_5.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Tablets to indicate that they are to be chewed before swallowing.

Identification—A 1 in 10 suspension of powdered Tablets in 3 *N* hydrochloric acid responds to the tests for *Aluminum* ⟨191⟩ and for *Sodium* ⟨191⟩.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.8(0.0208D),$$

in which 0.0208 is the theoretical acid-neutralizing capacity, in mEq, of CH_2AlNaO_5, and D is the quantity, in mg, of CH_2AlNaO_5 in the specimen tested, based on the labeled quantity.

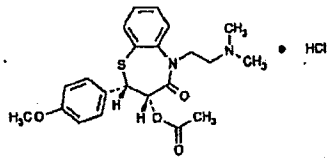
Assay—

Edetate disodium titrant—Dissolve 18.6 g of edetate disodium in water to make 500 mL, and standardize as directed in the *Assay* under *Alum*.

Procedure—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of dihydroxyaluminum sodium carbonate, to a 250-mL beaker, and proceed as directed in the *Assay for aluminum oxide* under *Dihydroxyaluminum Sodium Carbonate*, beginning with "add 10 mL of 2 *N* nitric acid." Each mL of 0.1 *M Edetate disodium titrant* is equivalent to 14.40 mg of CH_2AlNaO_5.

Diltiazem Extended-release Capsules—*see* Diltiazem Hydrochloride Extended-release Capsules

Diltiazem Hydrochloride



$C_{22}H_{26}N_2O_4S \cdot HCl$ 450.99

1,5-Benzothiazepin-4(5*H*)-one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-*cis*-.

(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one acetate (ester) monohydrochloride [*33286-22-5*].

» Diltiazem Hydrochloride contains not less than 98.5 percent and not more than 101.5 percent of $C_{22}H_{26}N_2O_4S \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Diltiazem Hydrochloride RS*. *USP Desacetyl Diltiazem Hydrochloride RS*.

Identification—
A: *Infrared Absorption* ⟨197K⟩.
B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation* obtained as directed in the *Assay*.
C: It responds to the tests for *Chloride* ⟨191⟩.

Specific rotation ⟨781S⟩: between +110° and +116°.
Test solution: 10 mg per mL, in water.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals ⟨231⟩: not more than 20 ppm.

Related compounds—
Buffer and *Mobile phase*—Prepare as directed in the *Assay*.
Standard solution—Use the *System suitability preparation* prepared as directed under *Assay*.
Test solution—Prepare as directed for the *Assay preparation* in the *Assay*.
Chromatographic system—Prepare as directed under *Assay*. The relative standard deviation of the peak response for replicate injections of the *Standard solution* is not more than 10.0%.
Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. The relative retention times are about 0.65 for desacetyl diltiazem and 1.0 for diltiazem. Calculate the percentage of desacetyl diltiazem hydrochloride in the specimen of Diltiazem Hydrochloride taken by the formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Desacetyl Diltiazem Hydrochloride RS in the *Standard solution*, W is the weight, in mg, of Diltiazem Hydrochloride taken, and r_U and r_S are the desacetyl diltiazem peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% of desacetyl diltiazem hydrochloride is found. Calculate the percentage of each impurity peak, other than the main peak and the desacetyl diltiazem peak, by the formula:

$$10(C/W)(r_I/r_S),$$

in which r_I is the response of each impurity peak and all other quantities are as defined above: not more than 1.0% total impurities including desacetyl diltiazem hydrochloride with no individual impurity greater than 0.5% is found.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay—
Buffer—Dissolve 1.16 g of *d*-10-camphorsulfonic acid in 1000 mL of 0.1 *M* sodium acetate, adjust this solution by the addition of 0.1 *N* sodium hydroxide to a pH of 6.2, and mix.
Mobile phase—Prepare a mixture of *Buffer*, acetonitrile, and methanol (50:25:25), filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard preparation—Prepare a solution in methanol having an accurately known concentration of about 1.2 mg of USP Diltiazem Hydrochloride RS per mL.
Assay preparation—Transfer about 120 mg of Diltiazem Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in methanol, dilute with methanol to volume, and mix.
System suitability preparation—Prepare a solution in methanol containing 0.012 mg each of USP Diltiazem Hydrochloride RS and USP Desacetyl Diltiazem Hydrochloride RS per mL.
Chromatographic system—The liquid chromatograph is equipped with a 240-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.6 mL per minute. Chromatograph the *System suitability preparation*, and record the peak responses as directed under *Procedure:* the relative retention times are about 0.65 for desacetyl diltiazem and 1.0 for diltiazem, the resolution, R, between desacetyl diltiazem and diltiazem is not less than 3, and the number of theoretical plates, n, for the diltiazem peak is not less than 1200. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.
Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{26}N_2O_4S \cdot HCl$ in the Diltiazem Hydrochloride taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation*, and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Diltiazem Hydrochloride Extended-release Capsules

» Diltiazem Hydrochloride Extended-release Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Diltiazem Hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

Packaging and storage—Preserve in tight containers.
USP Reference standards ⟨11⟩—*USP Diltiazem Hydrochloride RS. USP Desacetyl Diltiazem Hydrochloride RS.*

Identification—
A: Transfer 17.4 g of ammonium thiocyanate and 2.8 g of cobalt chloride to a 100-mL volumetric flask, add about 50 mL of water, and sonicate for 10 minutes. Dilute with water to volume, and mix (*Indicator solution*). Grind the contents of 1 Capsule, and transfer to a 15-mL screw-capped test tube. Add 10 mL of 0.1 *N* hydrochloric acid, shake, and filter. Add 2 mL of *Indicator solution* to 2 mL of the filtrate, and shake. Add 5 mL of chloroform, and shake: a blue color develops in the chloroform layer.
B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation* obtained as directed in the *Assay*.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—
Buffer—Dissolve 6.9 g of monobasic potassium phosphate in 1000 mL of water, adjust with 0.1 *N* hydrochloric acid to a pH of 3.0, add 0.50 mL of triethylamine, and mix.
Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard preparation—Prepare a solution in methanol having an accurately known concentration of about 1.2 mg of USP Diltiazem Hydrochloride RS per mL and a concentration of about 0.02 mg of USP Desacetyl Diltiazem Hydrochloride RS per mL. Pipet a 2.0-mL aliquot of this solution into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 0.024 mg of USP Diltiazem Hydrochloride RS per mL.
Assay preparation—Weigh and mix the contents of not less than 20 Capsules. Grind the contents thoroughly, and transfer an accurately weighed portion, equivalent to about 120 mg of diltiazem hydrochloride, to a 100-mL volumetric flask. Add approximately 60 mL of methanol, and shake by mechanical means for 30 minutes. Sonicate the resulting solution for 10 minutes to complete the extraction. Dilute with methanol to volume, and mix. Pipet a 2.0-mL aliquot into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, mix, and filter.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the relative retention times are about 0.7 for desacetyl diltiazem and 1.0 for diltiazem, the resolution, R, between desacetyl diltiazem and diltiazem is not less than 2.0, and

the relative standard deviation for replicate injections is not more than 2.0% for diltiazem.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{26}N_2O_4S \cdot HCl$ in the portion of Capsules taken by the formula:

$$5000C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation*, and r_U and r_S are the diltiazem peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Diltiazem Hydrochloride Tablets

» Diltiazem Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$).

Packaging and storage—Preserve in tight, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Diltiazem Hydrochloride RS. USP Desacetyl Diltiazem Hydrochloride RS.*

Identification—

A: Tablets respond to *Identification* test *A* under *Diltiazem Hydrochloride Extended-release Capsules.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Times: 30 minutes and 3 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 240 nm using filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same medium.

Tolerances—Use the following acceptance criteria for the 30-minute time point: at S_1 no unit is more than Q; at S_2 the average value is equal to or less than Q, and no unit is greater than Q + 10%; at S_3 the average value is equal to or less than Q, and not more than 2 units are more than Q + 10%, and no unit is more than Q + 25%. Use the criteria in the *Acceptance Table* under *Dissolution* ⟨711⟩ for the 3-hour time point. Not more than 60% (Q) of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ is dissolved in 30 minutes, and not less than 80% (Q) is dissolved in 3 hours.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Buffer, Mobile phase, Standard preparation, System suitability preparation, Chromatographic system, and *Procedure*—Proceed as directed in the *Assay* under *Diltiazem Hydrochloride.*

Assay preparation—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 600 mg of diltiazem hydrochloride to a 500-mL volumetric flask. Add 200 mL of methanol, sonicate for 1 hour, cool, dilute with methanol to volume, and mix. Centrifuge a 25-mL aliquot at 3500 rpm for 15 minutes and use the clear supernatant liquid for injection into the liquid chromatograph.

Procedure—Calculate the quantity, in mg, of $C_{22}H_{26}N_2O_4S \cdot HCl$ in the portion of Tablets taken by the formula:

$$500C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation*, and r_U and r_S are the diltiazem hydrochloride peak areas in the *Assay preparation* and the *Standard preparation*, respectively.

Diltiazem Tablets—*see* Diltiazem Hydrochloride Tablets

Diluted Alcohol—*see* Alcohol, Diluted NF

Diluted Hydrochloric Acid—*see* Hydrochloric Acid, Diluted NF

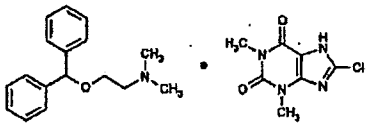
Diluted Isosorbide Dinitrate—*see* Isosorbide Dinitrate, Diluted

Diluted Nitroglycerin—*see* Nitroglycerin, Diluted

Diluted Pentaerythritol Tetranitrate—*see* Pentaerythritol Tetranitrate, Diluted

Diluted Phosphoric Acid—*see* Phosphoric Acid, Diluted NF

Dimenhydrinate



$C_{17}H_{21}NO \cdot C_7H_7ClN_4O_2$ 469.97

1*H*-Purine-2,6-dione, 8-chloro-3,7-dihydro-1,3-dimethyl-, compd. with 2-(diphenylmethoxy)-*N*,*N*-dimethylethanamine (1:1).

8-Chlorotheophylline, compound with 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine (1:1) [*523-87-5*].

» Dimenhydrinate contains not less than 53.0 percent and not more than 55.5 percent of diphenhydramine ($C_{17}H_{21}NO$), and not less than 44.0 percent and not more than 47.0 percent of 8-chlorotheophylline ($C_7H_7ClN_4O_2$), calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Dimenhydrinate RS.*

Identification—

A: It meets the requirements under *Identification—Organic Nitrogenous Bases* ⟨181⟩.

B: Dissolve about 250 mg in 15 mL of diluted alcohol, add 15 mL of water and 2 mL of 2 *N* sulfuric acid, and cool for 30 minutes. Scratch the inside of the container to facilitate crystallization. Filter the mixture, wash the crystals with a few mL of ice-cold water, and dry the crystals: the 8-chlorotheophylline melts between 300° and 305° with decomposition.

C: To about 10 mg of the 8-chlorotheophylline obtained in *Identification* test *B*, contained in a porcelain dish, add 1 mL of hydrochloric acid and 100 mg of potassium chlorate, evaporate on a steam bath to dryness, and invert the dish over a vessel containing a few drops of ammonia TS: the residue acquires a purple color, which is destroyed by solutions of fixed alkalies.

D: Mix about 50 mg of the 8-chlorotheophylline obtained in *Identification* test *B* with about 500 mg of sodium peroxide in a nickel crucible, and heat until the mass is well sintered. Dissolve the melt in 20 mL of water, acidify with 2 *N* nitric acid, filter if necessary, and add 1 mL of silver nitrate TS: a curdy, white precipitate is formed, and it is soluble in 6 *N* ammonium hydroxide and reappears upon acidification with nitric acid.

Melting range ⟨741⟩: between 102° and 107°.

the cut ends of the lap, and take particular care to secure portions throughout the thickness of the lap. To avoid biased selection of long or short fibers, remove all fibers of the group pinched and do not allow them to slip from between the fingers.

From packages of not more than 4 ounces in weight, take 8 pinches, and from packages weighing more than 4 ounces and not more than 8 ounces, take 16 pinches, all well distributed.

Mix the pinches in pairs promiscuously, and combine each pair by gently drawing and lapping them in the fingers. Then divide each combined pair by splitting longitudinally into two approximately equal parts and utilize one part in the further mixing. (The other part may be discarded or reserved for any further tests or checks.)

Repeat the process described in the preceding paragraph with the successive halves of the bifurcated series until only 1 pinch, the final composite test portion, results. Gently parallel and straighten the fibers of the final composite test portion by drawing and lapping them in the fingers. Take care to retain all of the fibers, including as far as possible those of the neps (specks of entangled fibers) and naps (matted masses of fibers), discarding only motes (immature seed fragments with fibers) and nonfiber foreign material such as stem, leaf, and fragments of seedcoats.

From the final composite portion described in the preceding paragraph, separate longitudinally a test portion of 75 ± 2 mg, accurately weighed. Retain the residue for any check test necessary.

Procedure—With the fiber-depressing grid carefully insert the weighed test portion into one bank of combs of the cotton sorter, so that it extends across the combs at approximately right angles.

With the sorter forceps, grip by the free ends a small portion of the fibers extending through the teeth of the comb nearest to the operator; gently and smoothly draw them forward out of the combs, and transfer them to the tips of the teeth in the second bank of combs, laying them parallel to themselves, straight, and approximately at right angles to the faces of the combs, releasing the gripped ends as near to the face of the front comb as possible. With the depressor grid carefully press the transferred fibers down into the teeth of the combs. Continue the operation until all of the fibers are transferred to the second bank of combs. During this transfer of the fibers, drop the combs of the first bank in succession when and as all of the protruding fibers have been removed.

Turn the machine through 180°, and transfer the cotton fibers back to the *first bank* of combs in the manner described in the preceding paragraph.

Take great care in evening up the ends of the fibers during both of the above transfers, arranging them as closely as possible to the front surface of the proximal comb. Such evening out of the ends of the protruding fibers may involve drawing out straggling fibers from both the front and rear aspects of the banks of combs, and re-depositing them into and over the main bundle in the combs.

Turn the machine again through 180°. Drop successive combs if necessary to expose the ends of the longest fibers. It may be necessary to re-deposit some straggling fibers. With the forceps withdraw the few most protuberant fibers. In this way continue to withdraw successively the remaining protuberant fibers back to the front face of the proximal comb. Drop this comb and repeat the series of operations in the same manner until all of the fibers have been drawn out. In order not to disturb seriously the portion being tested, and thereby vitiate the length fractionation into length groups, make several pulls (as many as 8 to 10) between each pair of combs.

Lay the pulls on the velvet-covered plates alongside each other, as straight as possible, with the ends as clearly defined as possible, and with the distal ends arranged in a straight line, pressing them down gently and smoothly with the fiber-depressing smooth plate before releasing the pull from the forceps. Employ not less than 50 and not more than 100 pulls to fractionate the test portion.

Group together all of the fibers measuring 12.5 mm (about ½ inch) or more in length, and weigh the group to the nearest 0.3 mg. In the same manner, group together all fibers 6.25 mm (about ¼ inch) or less in length, and weigh in the same manner. Finally, group the remaining fibers of intermediate lengths together and weigh. The sum of the three weights does not differ from the initial weight of the test portion by more than 3 mg. Divide the weight of each of the first two groups by the weight of the test portion to obtain the percentage by weight of fiber in the two ranges of length.

⟨695⟩ CRYSTALLINITY

This test is provided to determine compliance with the crystallinity requirement where stated in the individual monograph for a drug substance.

Procedure—Unless otherwise specified in the individual monograph, mount a few particles of the specimen in mineral oil on a clean glass slide. Examine the mixture using a polarizing microscope: the particles show birefringence (interference colors) and extinction positions when the microscope stage is revolved.

⟨698⟩ DELIVERABLE VOLUME

The following tests are designed to provide assurance that oral solutions and suspensions packaged in multiple-unit containers the labeled volume of which is not more than 250 mL, whether supplied as liquid preparations or liquid preparations that are constituted from solids upon the addition of a designated volume of a specific diluent, will, when transferred from the original container, deliver the volume of dosage form that is declared on the label of the article.

For the determination of deliverable volume, select not less than 30 containers, and proceed as follows for the dosage form designated.

ORAL SOLUTIONS, ORAL SUSPENSIONS, AND SYRUPS IN MULTIPLE-UNIT CONTAINERS—Mix the contents of 10 containers individually.

POWDERS IN MULTIPLE-UNIT CONTAINERS THAT ARE LABELED TO STATE THE VOLUME OF ORAL SOLUTION OR ORAL SUSPENSION THAT RESULTS WHEN THE POWDER IS CONSTITUTED WITH THE VOLUME OF DILUENT STATED IN THE LABELING—Constitute 10 containers with the volume of diluent stated in the labeling, accurately measured, and mix.

PROCEDURE—Gently pour the contents of each container into a separate dry graduated cylinder of a rated capacity not exceeding two and a half times the volume to be measured, and calibrated "to contain," being careful to avoid the formation of bubbles and allowing them to drain for a period not to exceed 30 minutes. When free from air bubbles, measure the volume of each mixture: the average volume of solution, suspension, or syrup obtained from the 10 containers is not less than 100%, and the volume of no container is less than 95% of the volume declared in the labeling. If *A*, the average volume is less than 100% of that declared in the labeling, but the volume of no container is less than 95% of the labeled amount, or *B*, the volume of not more than 1 container is less than 95%, but is not less than 90% of the labeled volume, perform the test on 20 additional containers. The average volume of solution, suspension, or syrup obtained from the 30 containers is not less than 100% of the volume declared in the labeling, and the volume of solution, suspension, or syrup obtained from not more than 1 of the 30 containers is less than 95%, but not less than 90% of that declared in the labeling.

⟨701⟩ DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms (see *Drug Release* ⟨724⟩). Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

Apparatus

The apparatus[1] consists of a basket-rack assembly, a 1000-mL, low-form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 7.75 ± 0.25 cm long and having an inside diameter of approximately 21.5 mm and a wall approximately 2 mm thick; the tubes are held in a vertical position by two plastic plates, each about 9 cm in diameter and 6 mm in thickness, with six holes, each about 24 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is 10-mesh No. 23 (0.025-inch) W. and M. gauge woven stainless-steel wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks[2]—The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a slotted and perforated cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2-mm holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes that are perpendicular to the ends of the cylinder. The dimensions of each notch are such that the openings on the bottom of the cylinder are 1.60 mm square and those on the top are 9.5 mm wide and 2.55 mm deep. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.

Procedure

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.

Enteric-coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable 10-mesh wire cloth,[3] as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.

[1] A suitable apparatus, meeting these specifications, is available from laboratory supply houses, from Van-Kel Industries, Inc., 36 Meridian Rd., Edison, NJ 08820, or from Hanson Research Corp., P. O. Box 35, Northridge, CA 91324.

[2] Disks meeting these specifications are obtainable from Van-Kel Industries, Inc.

[3] A suitable wire cloth cover is available as Van-Kel Industries Part TT-1030.

⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed unless otherwise directed in the monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. Of the types of apparatus described herein, use the one specified in the individual monograph.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS* (*Dissolution Calibrator, Nondisintegrating*). *USP Salicylic Acid Tablets RS* (*Dissolution Calibrator, Nondisintegrating*).

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size that permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom. It is 160 to 175 mm high, its inside diameter is 98 to 106 mm, and its nominal capacity is 1000 mL. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

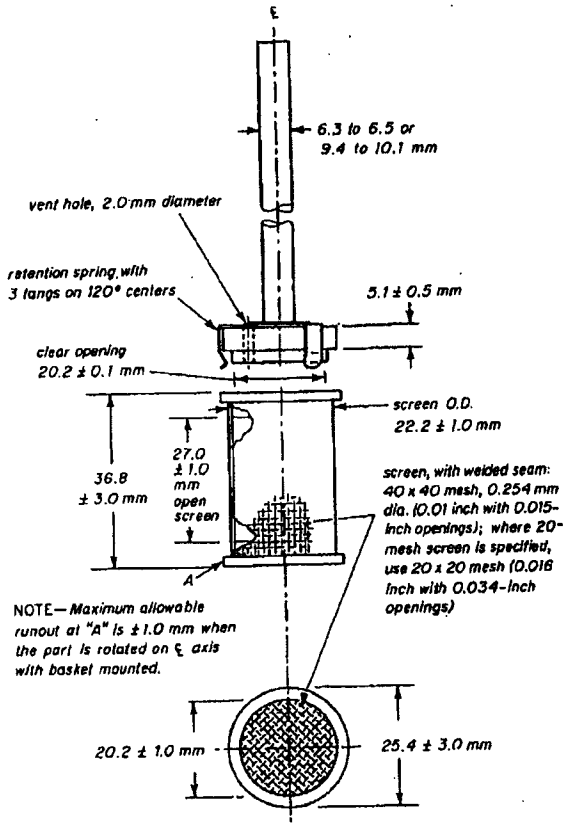


Fig. 1. Basket Stirring Element.

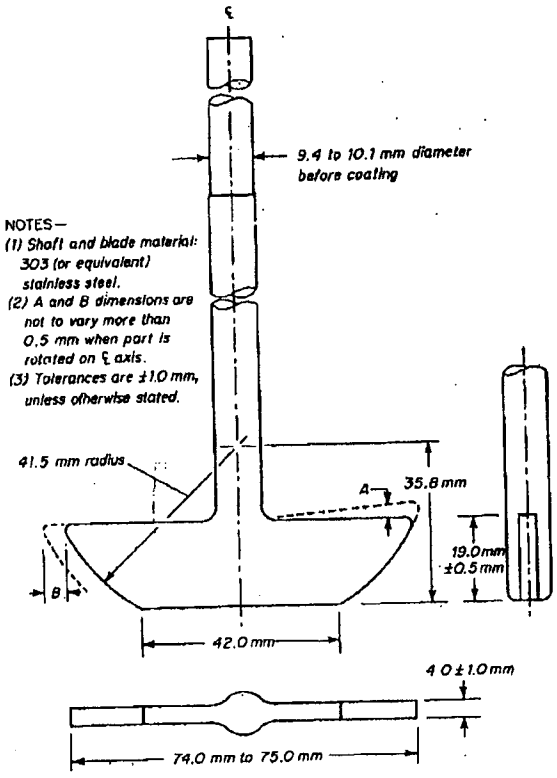


Fig. 2. Paddle Stirring Element.

positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel, and rotates smoothly without significant wobble. The blade passes through the diameter of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float.

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type* and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type*, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph.[4] Repeat the test with additional dosage form units.

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 45°, immediately filter under vacuum using a filter having a porosity of 0.45 μm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying acceptance table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; both the 5% and 15% values in the acceptance table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

METHOD I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper asbestos board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the asbestos has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.

METHOD II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Asbestos Boards—Two pieces of asbestos board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the contraction chamber (or bulb, if 37C or 38C is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.

⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph.

Apparatus 1 and Apparatus 2—

APPARATUS 1 AND APPARATUS 2—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.]

Extended-release Articles—General Drug Release Standard

Apparatus 3—

APPARATUS—The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and polypropylene screens that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. An apparatus that permits observation of the specimens and reciprocating cylinders is

preferable. The components conform to the dimensions shown in Figure 1 unless otherwise specified in the individual monograph.

Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage-form unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder, moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

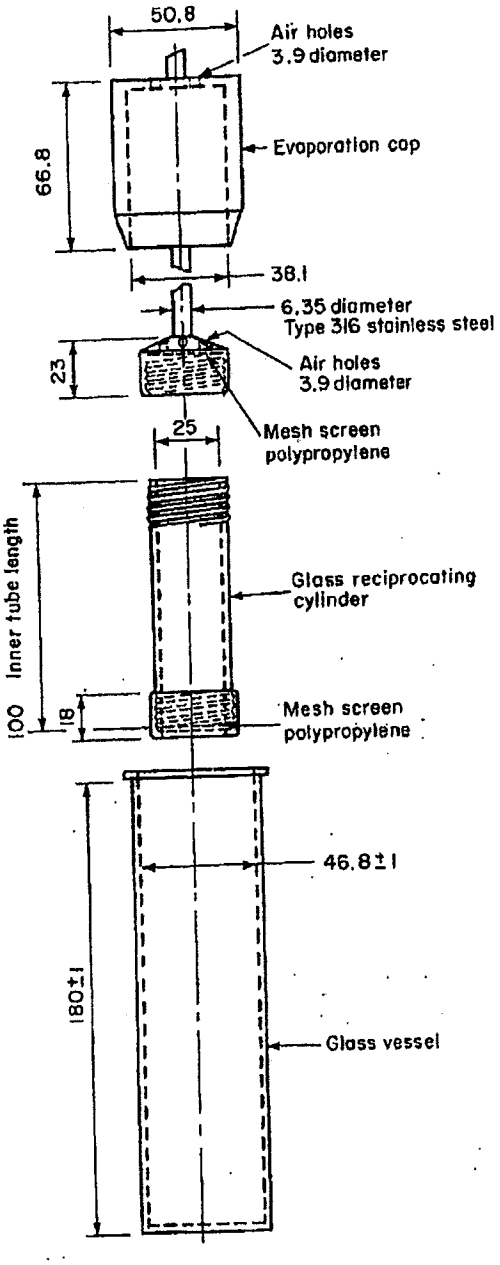


Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus 4—

APPARATUS—The assembly consists of a reservoir and a pump for the *Dissolution Medium;* a flow-through cell; a water bath that maintains the *Dissolution Medium* at 37 ± 0.5° (see Figures 2 and 3). The cell size is specified in the individual monograph.

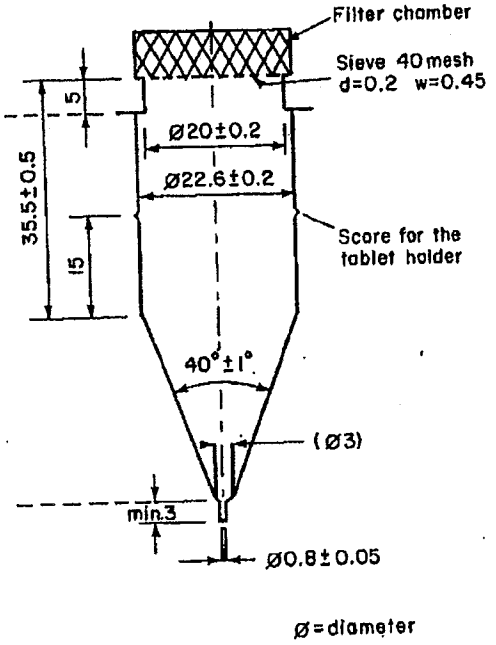


Fig. 2. Large cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

The pump forces the *Dissolution Medium* upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must be volumetric to deliver constant flow independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see Figures 2 and 3), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see Figures 2a and 3a) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath and the temperature is maintained at 37 ± 0.5°.

The apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump

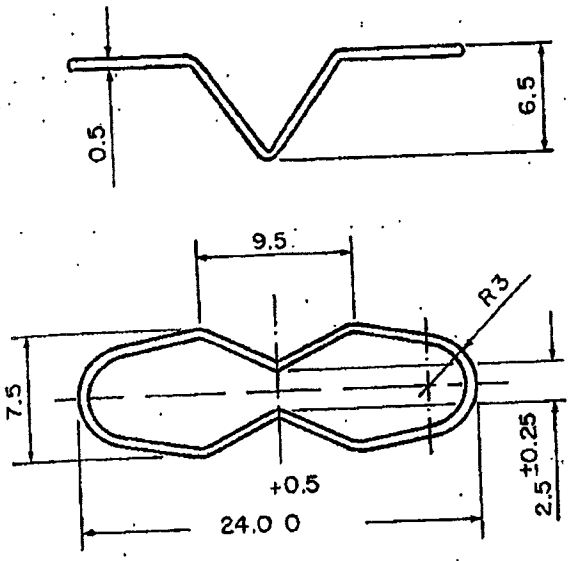


Fig. 2a. Tablet holder for the large cell. (All measurements are expressed in mm unless noted otherwise.)

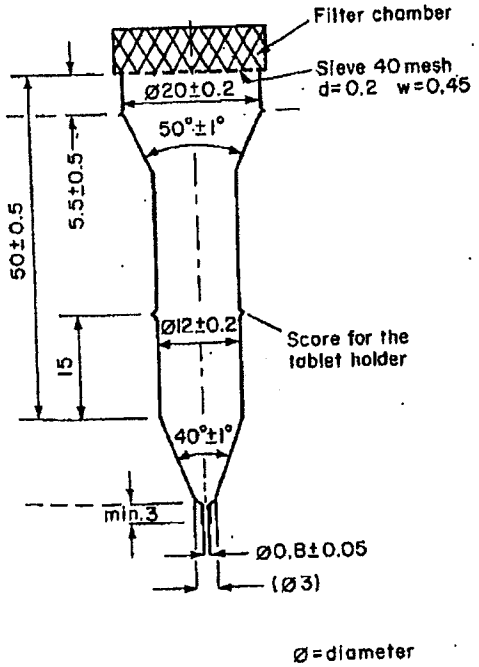


Fig. 3. Small cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use polytef tubing with a 1.6-mm inner diameter and chemically inert flanged-end connections.

Apparatus Suitability Test and Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

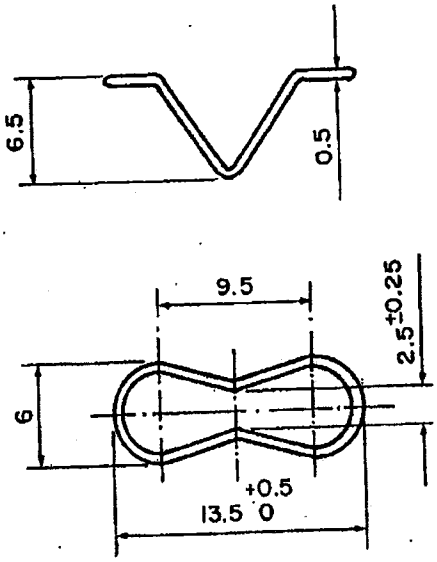


Fig. 3a. Tablet holder for the small cell. (All measurements are expressed in mm unless noted otherwise.)

Procedure—Place the glass beads into the cell specified in the monograph. Place 1 dosage-form unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval.

Delayed-release (Enteric-coated) Articles—General Drug Release Standard

Use *Method A* or *Method B* and the apparatus specified in the individual monograph. Conduct the *Apparatus Suitability Test* as directed under *Dissolution* ⟨711⟩. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 750 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 2

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—[NOTE—Complete the operations of adding the buffer, and adjusting the pH within 5 minutes.] With the apparatus operating at the rate specified in the monograph, add to the fluid in the vessel 250 mL of 0.20 *M* tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 *N* hydrochloric acid or 2 *N* sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of *Q* in *Acceptance Table 3* is 75% dissolved unless otherwise specified in the individual monograph. The quantity, *Q*, specified in the individual monograph, is the total amount of active ingredient dissolved in both the acid and buffer stages, expressed as a percentage of the labeled content. The 5% and 15% values in *Acceptance Table 3* are percentages of the labeled content so that these values and *Q* are in the same terms.

Acceptance Table 3

Level	Number Tested	Criteria
B_1	6	Each unit is not less than $Q + 5\%$.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

Method B:

Procedure (unless otherwise directed in the individual monograph)—

Acid Stage—Place 1000 mL of 0.1 *N* hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 tablet or 1 capsule in the apparatus, cover the vessel, and operate the apparatus for 2 hours at the rate specified in the monograph. After 2 hours of operation in 0.1 *N* hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using the *Procedure* specified in the test for *Drug release* in the individual monograph.

Unless otherwise specified in the individual monograph, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 2* under *Method A*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Buffer Stage—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 *N* hydrochloric acid with 0.20 *M* tribasic sodium phosphate (3:1) and adjusting, if necessary, with 2 *N* hydrochloric acid or 2 *N* sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may be accomplished also by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.] Continue to operate the apparatus for 45 minutes, or for the time specified in the individual monograph. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using the *Procedure* specified in the test for *Drug release* in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer stage* if the requirement for minimum amount dissolved is met at an earlier time.

Interpretation—Proceed as directed for *Interpretation* under *Method A*.

Transdermal Delivery Systems—General Drug Release Standards

Time—The test-time points, generally three, are expressed in terms of the labeled dosing interval, *D*, expressed in hours. Specimens are to be withdrawn within a tolerance of ± 15 minutes or ± 2% of the stated time, the tolerance that results in the narrowest time interval being selected.

Apparatus 5—

PADDLE OVER DISK—

APPARATUS—Use the paddle and vessel assembly from *Apparatus 2* as described under *Dissolution* ⟨711⟩, with the addition of a stainless steel disk assembly[1] designed for holding the transdermal system at the bottom of the vessel. The temperature is maintained at 32 ± 0.5°. A distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (see Figure 4).

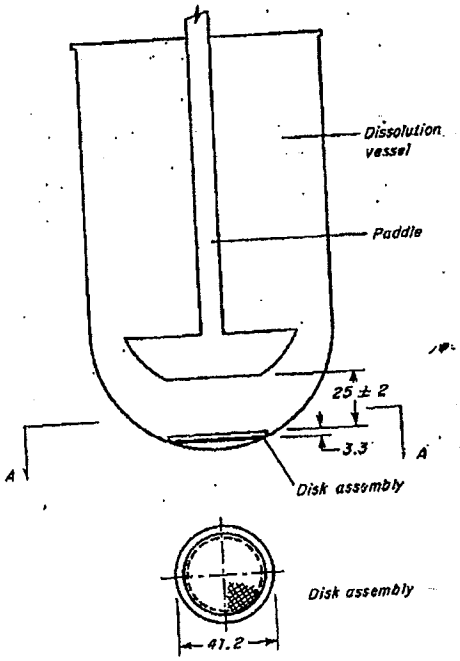


Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus Suitability Test and Dissolution Medium—Proceed as directed for *Apparatus 2* under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to 32 ± 0.5°. Apply the transdermal system to the disk assembly, assuring that the release surface of the system is as flat as possible. The system may be attached to the disk by applying a suitable adhesive[2] to the disk assembly. Dry for 1 minute. Press the system, release-surface side up, onto the adhesive-coated side of the disk assembly. If a membrane[3] is used to support the system, it is applied so that no air bubbles occur between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up and parallel to the edge of the paddle blade and surface of the *Dissolution Medium*. The bottom edge of the paddle is 25 ± 2 mm from the surface of the disk assembly. Immediately operate the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 4

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Apparatus 6—Cylinder—

APPARATUS—Use the vessel assembly from *Apparatus 1* as described under *Dissolution* ⟨711⟩, except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5° during the test. The shaft and cylinder components of the stirring element are fabricated of stainless steel to the specifications shown in Figure 5. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

Dissolution Medium—Use the medium specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to 32 ± 0.5°. Unless otherwise directed in the individual monograph, prepare the test system prior to test as follows. Remove the protective liner from the system, and place the adhesive side on a piece of Cuprophan[3] that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan covered side down, on a clean surface, and apply a suitable adhesive[2] to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 minute. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table*

[1] Disk assembly (stainless support disk) may be obtained from Millipore Corp., Ashley Rd., Bedford, MA 01730. Other appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being tested.

[2] Use Dow Corning, 355 Medical Adhesive 18.5% in Freon 113, or the equivalent.

[3] Use Cuprophan, Type 150 pm, 11 ± 0.5-μm thick, an inert, porous cellulosic material, which is available from ENKA AG, 1601 Castle Cove Circle, Corona DelMar, CA 92625, or LifeMed Corp., 2107 Delano Blvd., Compton, CA 90220.

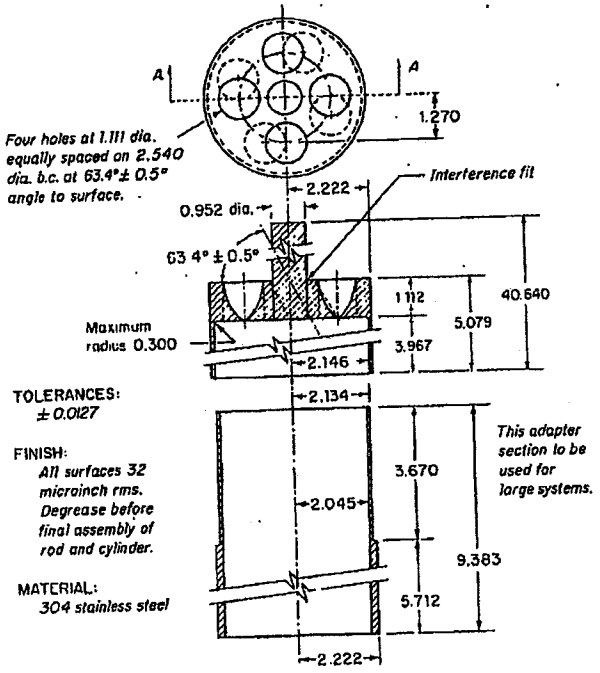


Fig. 5. Cylinder Stirring Element.[4] (All measurements are expressed in cm unless noted otherwise.)

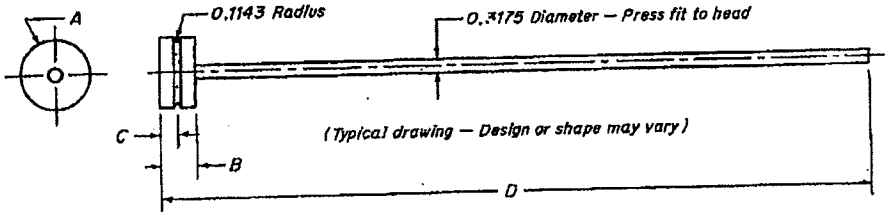
4 for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7—Reciprocating Disk—[NOTE—This apparatus may also be specified for use with solid oral dosage forms.]

APPARATUS—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material,[5] a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of disk-shaped sample holders (see Figure 6). The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature inside the containers at 32 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder. Apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder as specified in the individual monograph.

Dissolution Medium—Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Remove the transdermal system from its backing. Press the system onto a dry, unused piece of Cuprophan[3] or equivalent with the adhesive side against the Cuprophan, taking care to eliminate air bubbles between the Cuprophan and the release surface. Attach the system to a suitable size sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the sample holder. Trim the excess Cuprophan with a sharp blade. Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to 32 ± 0.5°. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 1.9 cm for the specified time in the medium specified for each time point. Perform the analysis as directed in the individual monograph. Repeat the test with additional transdermal drug delivery systems.



Dimensions are in centimeters.

System[a]	HEAD				ROD		O-RING
	A (Diameter)	B	C	Material[b]	D	Material[c]	(not shown)
1.6 cm²	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5 cm²	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5 cm²	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7 cm²	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10 cm²	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT = Either stainless steel or virgin Teflon.
[c] SS/P = Either stainless steel or Plexiglas.

Fig. 6. Reciprocating Disk Sample Holder.[6]

[4] The cylinder stirring element is available from Accurate Tool, Inc., 25 Diaz St., Stamford, CT 06907, or from Van-Kel Industries, Inc., 36 Meridian Rd., Edison, NJ 08820.

[5] The materials should not sorb, react with, or interfere with the specimen being tested.

[6] The reciprocating disk sample holder may be purchased from ALZA Corp., 950 Page Mill Rd., Palo Alto, CA 94304 or Van-Kel Industries, Inc.

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NOVEMBER 15, 1997

57 new monographs

New general tests chapters—
<699> Density of Solids
<786> Particle Size Distribution Estimation by Analytical Sieving

Revision of General Notices—Preservation, Packaging, Storage, and Labeling

Revision of general information chapter—<1151> Pharmaceutical Dosage Forms—Stability

Title changes to become official November 15, 1997 (and others on May 15, 1999) for several injectable dosage forms

Revisions of <11> USP Reference Standards — Up-to-date cumulative list and label text

IMPORTANT!
Save Supplement 1 and all succeeding Supplements

U. S. PHARMACOPEIA
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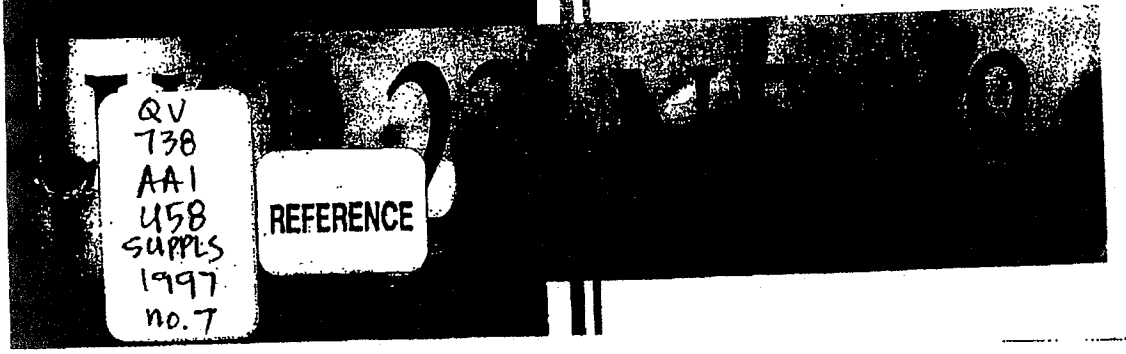
SUPPLEMENT



A-807

TS. Mix, add 2 drops of potassium ferricyanide TS, and observe after 2 minutes: no blue-green color develops.

Digoxin Tablets

Change to read:

Dissolution ⟨711⟩—[NOTE—Throughout this procedure, use scrupulously clean glassware, which previously has been rinsed successively with hydrochloric acid, water, and alcohol, and carefully dried. Take precautions to prevent contamination from fluorescent particles and from metal and rubber surfaces.]

Medium: 0.1 *N* hydrochloric acid; 500 mL. [NOTE—Use the same batch of *Dissolution Medium* throughout the test.]

Ascorbic acid–methanol—Prepare a solution containing 2 mg of ascorbic acid per mL of methanol.

Hydrogen peroxide–methanol—On the day of use, dilute 2.0 mL of recently assayed 30 percent hydrogen peroxide with methanol to 100 mL. Store in a refrigerator. Just prior to use, dilute 2.0 mL of this solution with methanol to 100 mL.

Standard solutions—Weigh accurately about 25 mg of USP Digoxin RS, dissolve in a minimum amount of alcohol in a 500-mL volumetric flask, add dilute alcohol (4 in 5) to volume, and mix. Dilute 10.0 mL of this solution with dilute alcohol (4 in 5) to 100.0 mL, and mix. Just prior to use, dilute suitable aliquots of the resulting solution with *Dissolution Medium* to 50.0 mL to prepare *Standard solutions* equivalent to 20%, 40%, 60%, 80%, and 100%, respectively, of the labeled amount of digoxin in 500 mL.

Apparatus 1: 120 rpm.

Time: 60 minutes.

Procedure—Filter a portion of the solution under test promptly after withdrawal, using a suitable membrane filter of not greater than 0.8 µm porosity, discarding the first 10 mL of the filtrate. This is the *Test solution*.

Measurement of fluorescence—Transfer to individual glass-stoppered flasks duplicate 1.0-mL portions of the *Test solution*, 1.0-mL portions of each of the *Standard solutions*, and 1.0 mL of the *Dissolution Medium* to provide a blank. Begin with the *Standard solutions*, and keep all flasks in the same sequence throughout, so that the elapsed time from addition of reagents to reading of fluorescence is the same for each flask in the set. Treating one flask at a time, add the following three reagents, in the order named, in as rapid a sequence as possible, swirling after each addition: 1.0 mL of *Ascorbic acid–methanol*, 5.0 mL of hydrochloric acid, and 1.0 mL of *Hydrogen peroxide–methanol*. Insert the stoppers in the flasks, and after 2 hours, measure the fluorescence at about 485 nm, the excitation wavelength being about 372 nm. To check the stability of the fluorometer, repeat the measurement of fluorescence on one or more treated *Standard solutions*. Correct each reading for the blank, and plot a standard curve of fluorescence versus percentage dissolution. Determine the percentage dissolution of digoxin in the *Test solution* by reading from the standard graph.

Tolerances—■ Not less than 80% (*Q*) of the labeled amount of $C_{41}H_{64}O_{14}$ is dissolved in 60 minutes. ■

Dihydrocodeine Bitartrate

Change to read:

Identification—

A: The chromatogram of the *Assay preparation* obtained as directed in the *Assay* exhibits a major peak for dihydrocodeine, the retention time of which corresponds to that in the chromatogram of the *Standard preparation* similarly determined.

B: It responds to the tests for *Tartrate* ⟨191⟩.

C: To a solution of 20 mg in 5 mL of sulfuric acid in a test tube add 1 drop of ferric chloride TS, and heat in a boiling water bath for 2 minutes: ■although the solution may darken, no blue color is produced■ (*distinction from codeine and morphine*).

Change to read:

pH ⟨791⟩: between ■3.2 and 4.2■ in a solution (1 in ■10).■

Diltiazem Hydrochloride Extended-release Capsules

Add the following:

■**Labeling**—The labeling indicates the *Drug Release Test* with which the product complies.■

Change to read:

■**Drug release** ⟨724⟩—

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1*. Proceed as directed for *Extended-release Articles—General Drug Release Standard* ⟨724⟩.

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Times: 3 hours, 9 hours, 12 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 237 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same medium.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to the *Acceptance Table* given.

Time (hours)	Amount dissolved
3	between 10% and 25%
9	between 45% and 85%
12	not less than 70%

Acceptance Table

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours none of the units is outside the range of 10% to 35% of labeled content; at 9 hours none of the units is outside the range of 45% to 95% of labeled content; and at 12 hours none of the units is less than 65% of labeled content at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours not more than 2 of the 24 units are outside the range of 10% to 35% of labeled content, and these two units must be within the range of 5% to 45% of labeled content; at 9 hours not more than 2 of 24 of the units are outside the range of 45% to 95% of labeled content, and these two units must be within the range of 35% to 100% of labeled content; at 12 hours not more than 2 of the 24 units are less than 65% of labeled content at the final test time, and these two units cannot be less than 60% of labeled content at the final test time.

•*Test 4:* If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 4.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times and tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
4	between 10% and 25%
8	between 35% and 60%
12	between 55% and 80%
24	not less than 80%

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5.*

Medium: 0.05 *M* phosphate buffer, pH 7.2; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times and tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
1	not more than 15%
3	between 45% and 70%
8	not less than 80%•5

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times and tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 70% and 90%
15	not less than 80%

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3.*

Medium: 0.1 *N* hydrochloric acid; 900 mL.

Apparatus 2: 100 rpm.

Times: 6 hours, 12 hours, 18 hours, 24 hours, 30 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 237 nm of filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same medium.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 85%■

•*Test 6:* If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 6.*

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1.*

Times and Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1* under *Drug release* ⟨724⟩.

Time (hours)	Amount dissolved
2	not more than 25%
4	between 25% and 55%
6	between 45% and 75%
10	between 65% and 95%
22	not less than 80%•16

Diltiazem Hydrochloride Tablets

Delete the following:

■ •**Labeling**—The labeling indicates the *Dissolution Test* with which the product complies.•10 ■7

Change to read:

Dissolution ⟨711⟩—

■ ■7

Medium: water; 900 mL.

Apparatus 2: ■75■7 rpm.

Times: 30 minutes and 3 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 240 nm using filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same medium.

Tolerances—Use the following acceptance criteria for the 30-minute time point: at S_1 no unit is more than Q; at S_2 the average value is equal to or less than Q, and no unit is greater than Q + 10%; at S_3 the average value is equal to or less than Q, and not more than 2 units are more than Q + 10%, and no unit is more than Q + 25%. Use the criteria in the *Acceptance Table* under *Dissolution* ⟨711⟩ for the 3-hour time point. Not more than 60% (Q) of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ is dissolved in 30 minutes, and not less than ■75%■7 (Q) is dissolved in 3 hours.

■ ■7

Doxycycline Hyclate

Change to read:

Water, *Method I* ⟨921⟩: between 1.4% and ■2.8%.■7

Change to read:

Assay—

Mobile phase—■Transfer 2.72 g of monobasic potassium phosphate, 0.74 g of sodium hydroxide, 0.50 g of tetrabutylammonium hydrogen sulfate, and 0.40 g of edetate disodium to a 1000-mL volumetric flask. Add about 850 mL of water, and stir to dissolve. Add 60 g of tertiary butyl alcohol with the aid of water, dilute with water to volume, and adjust with 1 *N* sodium hydroxide to a pH of 8.0 ± 0.1. Filter this solution through a filter of 0.5 µm or finer porosity and degas before using. Make any necessary adjustments (see *System Suitability* under *Chromatography* ⟨621⟩). Decreasing the proportion of tertiary butyl alcohol results in a longer retention time of doxycycline and improved separation of doxycycline from the related compounds.

Diluent—Use 0.01 *N* hydrochloric acid.

Resolution solution—Prepare a solution of USP Doxycycline Hyclate RS in *Diluent* containing about ■6 mg■5 of doxycycline per mL. Transfer 5 mL of this solution to a 25-mL volumetric flask, heat on a steam bath for 60 minutes, and evaporate to dryness on a hot plate, taking care not to char the residue. Dissolve the residue in 0.01 *N* hydrochloric acid, dilute with *Diluent* to volume, and mix. Filter a portion of this solution through a filter having a porosity of 0.5 µm or finer, and use the filtrate as the *Resolution solution.* This solution contains a mixture of 4-epidoxycycline, 6-epidoxycycline, and doxycycline. When stored in a refrigerator, this solution may be used for 14 days.■4

[NOTE—Throughout the following sections, protect the *Standard preparation* and the *Assay preparation* from light.]

Standard preparation—■Transfer about 30 mg of USP Doxycycline Hyclate RS, accurately weighed, to a 25-mL volumetric flask, add about 15 mL of *Diluent,* sonicate for about 5 minutes or until dissolved, dilute with *Diluent* to volume, and mix.■4

Assay preparation—Transfer about 120 mg of Doxycycline Hyclate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with ■*Diluent*■4 to volume, and mix. Filter through a membrane filter of 0.5 µm or finer porosity.

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92 new monographs

Botanicals—Feverfew; Ginkgo; Oriental Ginseng; St. John's Wort; Chamomile; Saw Palmetto—9 monographs

Compounded preparations—Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution; Hydralazine Hydrochloride Oral Solution; Rifampin Oral Suspension; Sodium Hypochlorite Topical Solution

Title changes to become official November 15, 1998 (and others on January 1, 2000) for several injectable dosage forms

Revisions of <11> USP Reference Standards —Up-to-date cumulative list and label text

IMPORTANT!
Save Supplement 1 and all succeeding Supplements

Change to read:

■REPACKAGING INTO SINGLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR NONSTERILE SOLID AND LIQUID DOSAGE FORMS■

An official dosage form is required to bear on its label an expiration date assigned for the particular formulation and package of the article. This date limits the time during which the product may be dispensed or used. Because the expiration date stated on the manufacturer's or distributor's package has been determined for the drug in that particular package and ■is not intended■ to be applicable to the product where it has been repackaged in a different container, repackaged drugs dispensed pursuant to a prescription are exempt from this ■expiration date labeling■ requirement. It is necessary, therefore, that other precautions be taken by the dispenser to preserve the strength, quality, and purity of drugs that are repackaged for ultimate distribution or sale to patients.

The following guidelines and requirements are applicable where official dosage forms are repackaged into single-unit or unit-dose containers or mnemonic packs for dispensing pursuant to prescription.

Labeling—It is the responsibility of the dispenser, taking into account the nature of the drug repackaged, ■any packaging and beyond-use dating information in the manufacturer's product labeling,■ the characteristics of the containers, and the storage conditions to which the article may be subjected, to ■place■ a suitable beyond-use date on the label. ■Repackaged dosage forms must bear on their labels beyond-use dates as determined from information in the product labeling.■ In the absence of stability data ■or information■ to the contrary, such date should not exceed (1) 25% of the remaining time between the date of repackaging and the expiration date on the original manufacturer's bulk container, or (2) a six-month period from the date the drug is repackaged, whichever is earlier. Each single-unit or unit-dose container bears a separate label, unless the device holding the unit-dose form does not allow for the removal or separation of the intact single-unit or unit-dose container therefrom.

Storage—Store the repackaged article in a humidity-controlled environment and at the temperature specified in the individual monograph or in the product labeling. Where no temperature or humidity is specified in the monograph or in the labeling of the product, controlled room temperature and a relative humidity corresponding to 75% at 23° are not to be exceeded during repackaging or storage.

A refrigerator or freezer shall not be considered to be a humidity-controlled environment, and drugs that are to be stored at a cold temperature in a refrigerator or freezer shall be placed within an outer container that meets the monograph requirements for the drug contained therein.

⟨701⟩ DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms (see *Drug Release* ⟨724⟩). Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

Change to read:

APPARATUS

The apparatus ■■ consists of a basket-rack assembly, a 1000-mL, low-form beaker, ■ ■142 to 148 mm■ in height and having an outside diameter of ■103 to 108 mm■ ■ for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 7.75 ± 0.25 cm long and having an inside diameter of ■20.7 to 23 mm■ and a wall ■1.0 to 2.8 mm■ thick; the tubes are held in a vertical position by two plastic plates, each ■8.8 to 9.2 cm■ in diameter and ■5 to 7 mm■ in thickness, with six holes, each ■22 to 26 mm■ in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is ■a■ ■woven stainless steel wire cloth, ■which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm.■ ■ The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks ■■—The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a ■■ cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. ■Five parallel 2-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 mm from the axis on imaginary lines perpendicular to the axis and ■parallel■ to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 mm, and its center lies at a depth of 1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.2 mm, and its center lies at a depth of 2.6 mm from the cylinder's circumference.■ All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.

Delete the following:

■[1] A suitable apparatus, meeting these specifications, is available from laboratory supply houses, from VanKel Industries, Inc., 36 Meridian Rd., Edison, NJ 08820, or from Hanson Research Corp., P. O. Box 35, Northridge, CA 91324.■

Delete the following:

■ ■■ A suitable wire cloth cover is available as VanKel Industries ■Part 10.1030.■■

Delete the following:

■ ■■ Disks meeting these specifications are obtainable from VanKel Industries, Inc.■

(Nomenclature related changes—to become official May 15, 1999)

Change to read:

PROCEDURE

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.

Enteric Coated Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

(The above *Enteric Coated Tablets* section is official until May 15, 1999)

Change to read:

Delayed-release (enteric coated) Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

(The above *Delayed-release (enteric coated) Tablets* section will become official May 15, 1999)

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.

⟨711⟩ DISSOLUTION

Change to read:

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. For hard gelatin capsules that do not conform to the *Dissolution* specification, repeat the test as follows. Where water is not specified as the *Medium* in the individual monograph, the same *Medium* specified in the monograph may be used with the addition of not more than 3.2 g of purified pepsin having an activity of 800 to 2500 units per mg of protein, or not more than 5 g of pancreatin, per 1000 mL of *Medium*, as appropriate. Pepsin is added to acidic media, while pancreatin is appropriate for media at or above a pH of 6.8. Where the monograph specifies water as the *Medium*, a second medium of either 0.1 *N* hydrochloric acid with pepsin or pH 6.8 phosphate buffer with pancreatin, depending on the drug solubility, may be used with the concentration of pepsin or pancreatin being the same as above.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS* (*Dissolution Calibrator, Disintegrating*). *USP Salicylic Acid Tablets RS* (*Dissolution Calibrator, Nondisintegrating*).

Change to read:

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 liter, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 liters, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 liters, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

Change to read:

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft, so that the bottom of the blade is flush with the bottom of the shaft. The paddle con-

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

forms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic ■or suitably inert, rigid■ blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. ■Other validated sinker devices may be used.■

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type* and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type*, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Change to read:

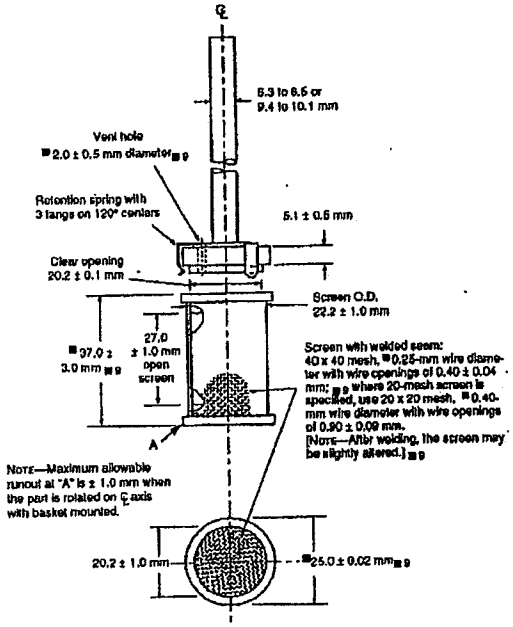


Fig. 1. Basket Stirring Element.

Change to read:

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about ■41°,■ immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

Change to read:

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* ■(±1%)■ in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph.[4] Repeat the test with additional dosage form units.

■If automated equipment is used for sampling and the apparatus is modified, validation of the modified apparatus is needed to show that there is no change in the agitation characteristics of the test.■

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Change to read:

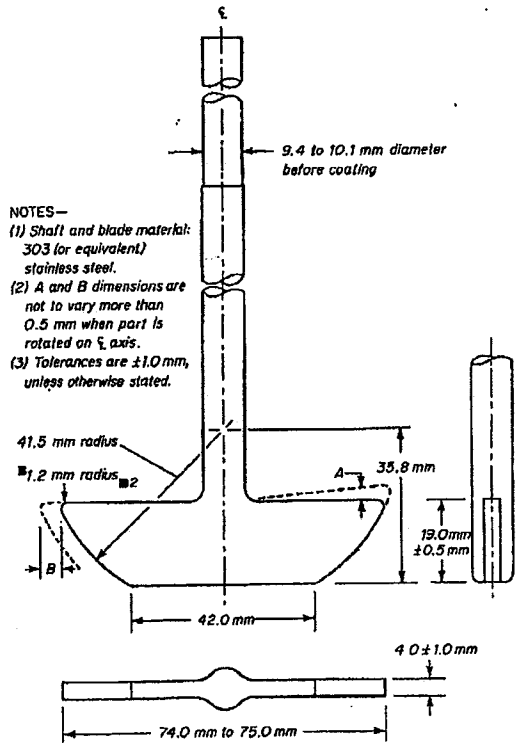


Fig. 2. Paddle Stirring Element.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

Change to read:

■**Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets**—Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed under *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets*. Combine equal volumes of the filtered solutions of the six ■or twelve■ individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of the active ingredient dissolved in the pooled sample.■

Change to read:

Interpretation—

■*Unit Sample*—■Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; ■■ the 5%, ■15%, and 25%■ values in the Acceptance Table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15\%$, and no unit is less than $Q - 25\%$.

■*Pooled Sample*—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.■

Add the following:

■**Acceptance Table for a Pooled Sample.**

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than $Q + 10\%$.
S_2	6	Average amount dissolved ($S_1 + S_2$) is equal to or greater than $Q + 5\%$.
S_3	12	Average amount dissolved ($S_1 + S_2 + S_3$) is equal to or greater than Q.■

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

Change to read:

Method I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper ■insulating■ board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the ■insulating material■ has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.

Change to read:

Method II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

■*Insulating■ Boards*—Two pieces of ■insulating■ board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the contraction chamber (or bulb, if 37C or 38C is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the ■observed ambient■ barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.

⟨724⟩ DRUG RELEASE

Change to read:

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. ■Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. [NOTE—Medium replacement is not necessary for *Apparatus 4*, which is a continuous-flow system.] Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.■

Change to read:

EXTENDED-RELEASE ARTICLES—GENERAL DRUG RELEASE STANDARD

Apparatus 1 and Apparatus 2

Apparatus ■■—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩.■■

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval. ■Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.■

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Apparatus 3 ■(Reciprocating Cylinder)■

Apparatus—The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and ■■ screens that are ■made of suitable nonsorbing and nonreactive material and that are■ designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. ■A device is used that allows the reciprocation rate to be selected and maintained at the dip rate specified in the individual monograph, within ±5%.■ An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The components conform to the dimensions shown in Figure 1 unless otherwise specified in the individual monograph.

■**USP Reference Standards** ⟨11⟩—*USP Chlorpheniramine Extended-release Tablets RS* (*Drug Release Calibrator, Single Unit*). *USP Theophylline Extended-release Beads RS* (*Drug Release Calibrator, Multiple Unit*).■

■**Apparatus Suitability Test**—Individually test 1 tablet of the USP Drug Release Calibrator Tablets (Single Unit) and a specified amount of beads of the USP Drug Release Calibrator Beads (Multiple Unit) according to the operation conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.■

Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage-form unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time and Interpretation—Proceed as directed under *Apparatus 1 and 2*.

Apparatus 4 ■(Flow-through Cell)■

Apparatus—The assembly consists of a reservoir and a pump for the *Dissolution Medium;* a flow-through cell; a water bath that maintains the *Dissolution Medium* at 37 ± 0.5° (see Figures 2 and 3). The cell size is specified in the individual monograph.

The pump forces the *Dissolution Medium* upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must be volumetric to deliver constant flow independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see Figures 2 and 3), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see Figures 2a and 3a) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature is maintained at 37 ± 0.5°.

The apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly. The pump is separated from the dis-

Change to read:

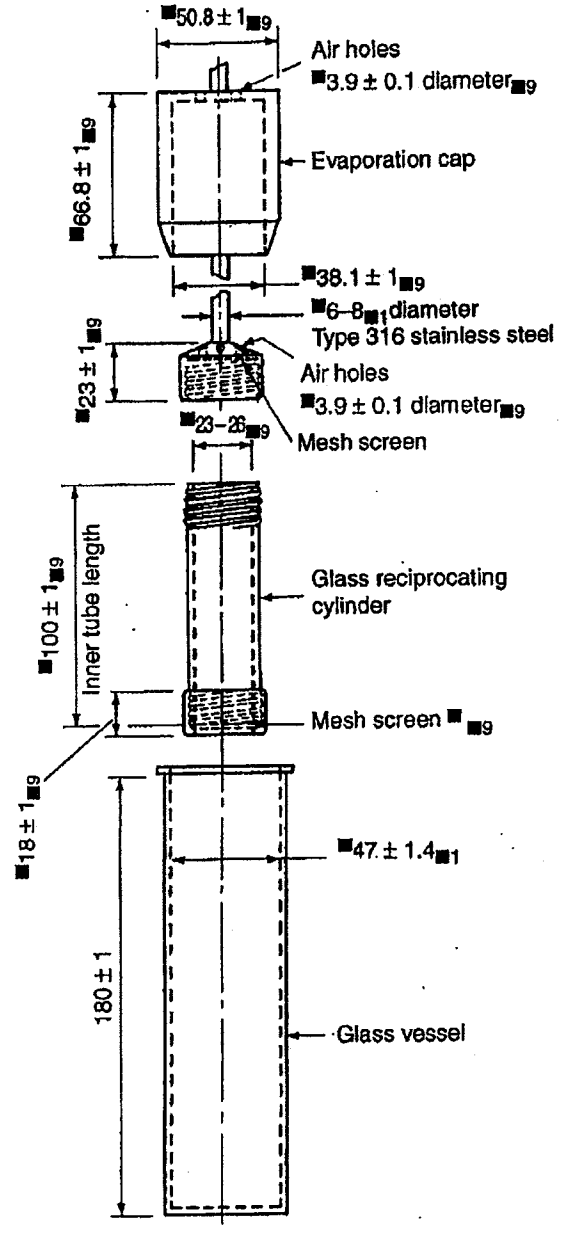


Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

solution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use polytef tubing with a 1.6-mm inner diameter and chemically inert flanged-end connections.

Apparatus Suitability Test and Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the glass beads into the cell specified in the monograph. Place 1 dosage-form unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time and Interpretation—Proceed as directed under *Apparatus 1 and 2*.

Change to read:

TRANSDERMAL DELIVERY SYSTEMS—GENERAL DRUG RELEASE STANDARDS

Apparatus 5 (Paddle over Disk)

Apparatus—Use the paddle and vessel assembly from *Apparatus 2* as described under *Dissolution* ⟨711⟩, with the addition of a stainless steel disk assembly[1] designed for holding the transdermal system at the bottom of the vessel. Other appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being tested[2]. The temperature is maintained at 32 ± 0.5°. A distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (see Figure 4).

Apparatus Suitability Test and Dissolution Medium—Proceed as directed for *Apparatus 2* under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to 32 ± 0.5°. Apply the transdermal system to the disk assembly, assuring that the release surface of the system is as flat as possible. The system may be attached to the disk by applying a suitable adhesive[3] to the disk assembly. Dry for 1 minute. Press the system, release surface side up, onto the adhesive-coated side of the disk assembly. If a membrane[4] is used to support the system, it is applied so that no air bubbles occur

Change to read:

[1] Disk assembly (stainless support disk) may be obtained from Millipore Corp., Ashley Rd., Bedford, MA 01730.

Add the following:

[2] A suitable device is the watchglass-patch-polytef mesh sandwich assembly available as the Transdermal Sandwich™ from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

Change to read:

[3] Use Dow Corning, 355 Medical Adhesive 18.5% in Freon 113, or the equivalent.

Change to read:

[4] Use Cuprophan, Type 150 pm, 11 ± 0.5-µm thick, an inert, porous cellulosic material, which is available from Medicell International Ltd., 239 Liverpool Road, London NI ILX, England.

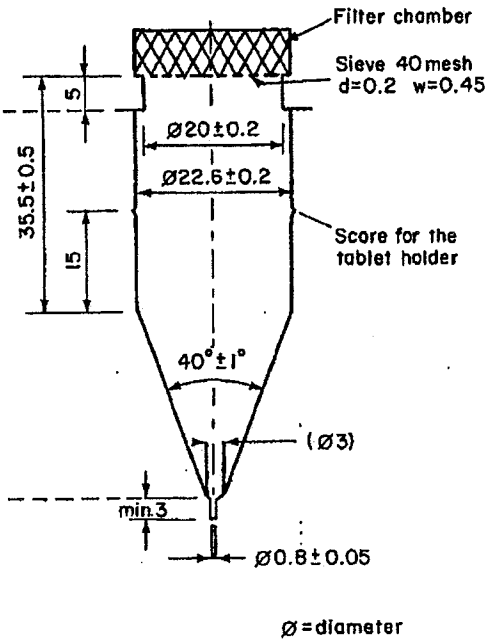


Fig. 2. Large cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

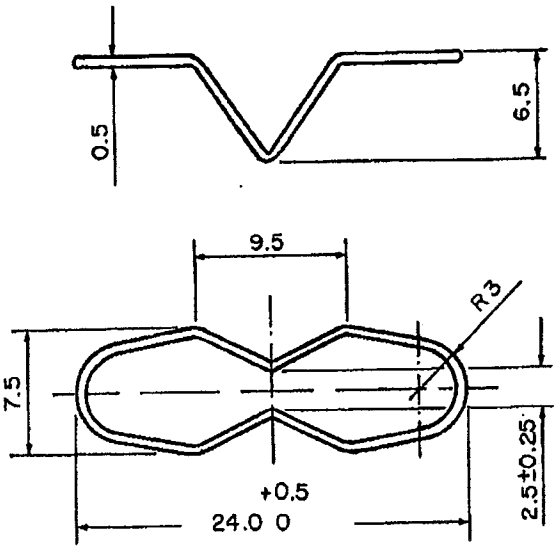


Fig. 2a. Tablet holder for the large cell. (All measurements are expressed in mm unless noted otherwise.)

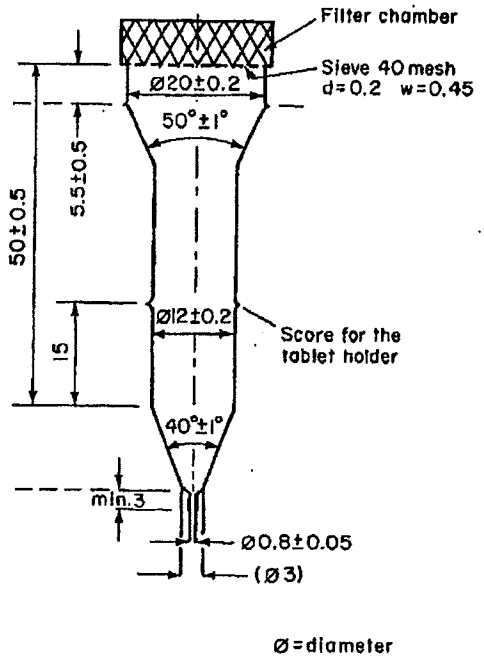


Fig. 3. Small cell for tablets and capsules. (All measurements are expressed in mm unless noted otherwise.)

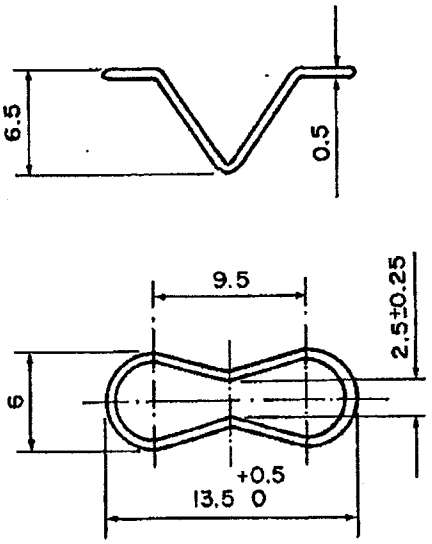


Fig. 3a. Tablet holder for the small cell. (All measurements are expressed in mm unless noted otherwise.)

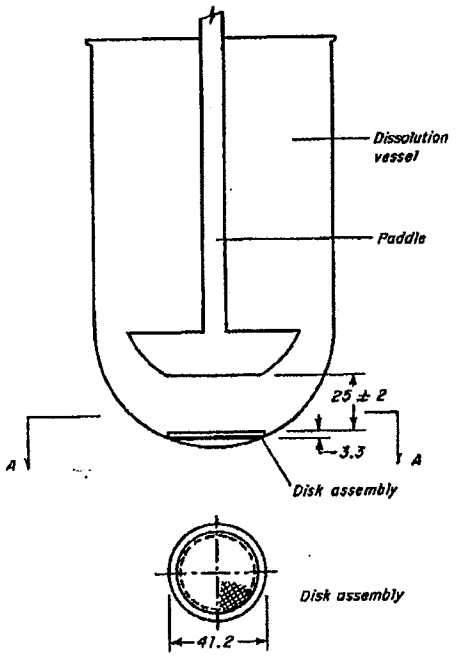


Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up and parallel to the edge of the paddle blade and surface of the *Dissolution Medium*. The bottom edge of the paddle is 25 ± 2 mm from the surface of the disk assembly. Immediately operate the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

Time—The test time points, generally three, are ■ ■, expressed in hours. Specimens are to be withdrawn within a tolerance of ±15 minutes or ±2% of the stated time, the tolerance that results in the narrowest time interval being selected.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 4

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Apparatus 6 (Cylinder)

Apparatus—Use the vessel assembly from *Apparatus 1* as described under *Dissolution* ⟨711⟩, except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5° during the test. The shaft and cylinder components of the stirring element are fabricated of stainless steel to the specifications shown in Figure 5. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

Dissolution Medium—Use the medium specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to 32 ± 0.5°. Unless otherwise directed in the individual monograph, prepare the test system prior to test as follows. Remove the protective liner from the system, and place the adhesive side on a piece of Cuprophan■ ■ that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan covered side down, on a clean surface, and apply a suitable adhesive■ ■ to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 minute. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

Time—Proceed as directed under *Apparatus 5*.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Apparatus 7 (Reciprocating ■Holder■)

NOTE—This apparatus may also be specified for use with ■a variety of■ dosage forms.

Apparatus—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material,■ ■ a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of ■suitable■ sample holders (see Fig. 6 ■and Figs. 7a–7d).■ The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, ■T,■ inside the containers at 32 ± 0.5° ■or within the allowable range, as specified in the individual monograph,■ during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder. Apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder as specified in the individual monograph.

Change to read:

■ ■ Use Dow Corning, 355 Medical Adhesive 18.5% in Freon 113, or the equivalent.

Change to read:

■ ■ Use Cuprophan, Type 150 pm, 11 ± 0.5-μm thick, an inert, porous cellulosic material, which is available from ■Medicell International Ltd., 239 Liverpool Road, London N1 1LX, England.■

Change to read:

■ ■ The materials should not sorb, react with, or interfere with the specimen being tested.

Change to read:

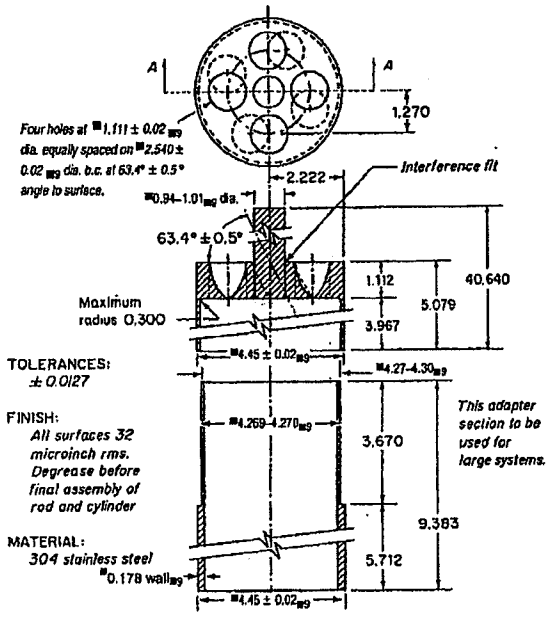


Fig. 5. Cylinder Stirring Element. ■5■5
(All measurements are expressed in cm unless noted otherwise.)

Change to read:

■5■5 The cylinder stirring element is available from Accurate Tool, Inc., 25 Diaz St., Stamford, CT 06907, or from VanKel Industries, Inc., 36 Meridian Rd., Edison, NJ 08820.

Dissolution Medium—Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* ⟨711⟩).

■**Sample Preparation A** (Coated tablet drug delivery system)—Attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the end of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

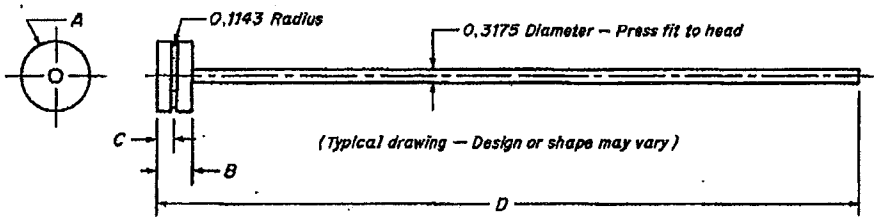
Sample Preparation B (Transdermal drug delivery system)—Press the system onto a dry, unused piece of Cuprophan■4,■5 nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitable sized sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

Sample Preparation C (Other drug delivery systems)—Attach each system to be tested to a suitable holder as described in the individual monograph.

■**Procedure**■3—Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to temperature, *T*. Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (i.e., water in most cases) to correct for evaporative losses. Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 1* for coated tablet drug delivery systems, to *Acceptance Table 4* for transdermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either L_1 or L_2.■2

Change to read:



Dimensions are in centimeters.

	HEAD				ROD		O-RING
System[a]	*A (Diameter)*	*B*	*C*	Material[b]	*D*	Material[c]	*(not shown)*
1.6 cm²	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5 cm²	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5 cm²	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7 cm²	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10 cm²	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT = Either stainless steel or virgin Teflon.
[c] SS/P = Either stainless steel or Plexiglas.

Fig. 6. Reciprocating Disk Sample Holder. [87s]

Change to read:

[87s] The reciprocating disk sample holder may be purchased from ALZA Corp., 950 Page Mill Rd., Palo Alto, CA 94304 or VanKel Industries, Inc.

Add the following:

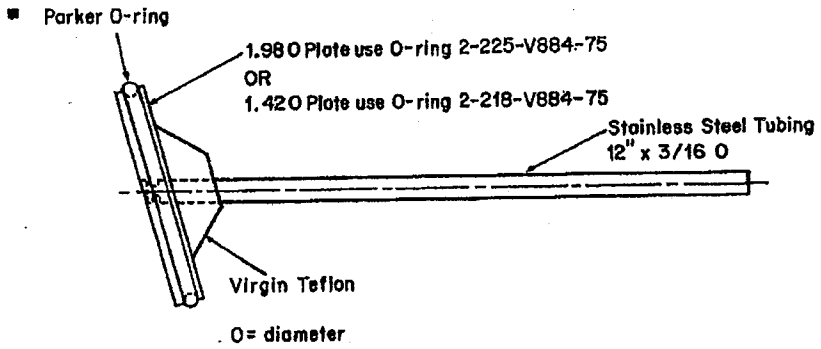


Fig. 7a. Transdermal system holder—angled disk.

Add the following:

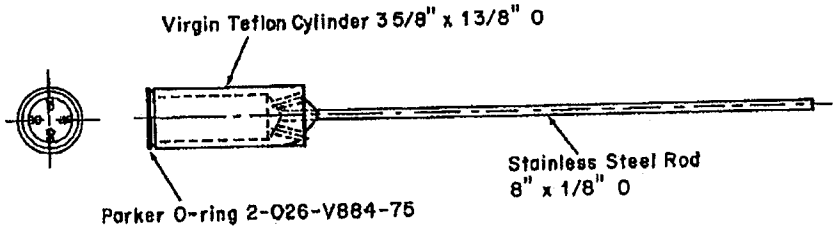


Fig. 7b. Transdermal system holder—cylinder.

Add the following:

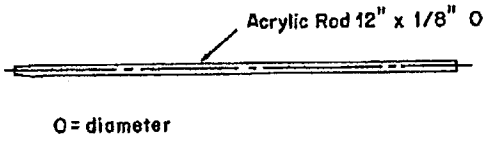
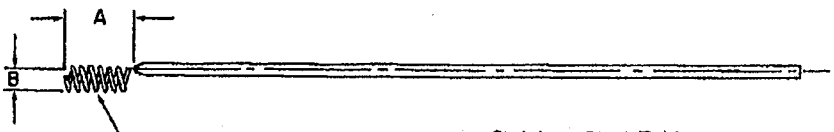


Fig. 7c. Oral extended-release tablet holder—rod, pointed for gluing.

Add the following:



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O= diameter

Fig. 7d. Oral extended-release tablet holder—spring holder.